REMARKS

Applicants acknowledge the withdrawal of objections and rejections of the prior Office Action as summarized by the Examiner on page 2 of the present Office Action.

Claim 1 has been amended to introduce a further first proviso in view of PCT published application WO 98/17679. The amended claim as well as claims dependent thereon, is thus clearly distinguished from this reference. Specifically, Formula I of claim 1 and all of its identified variations are not within the scope of the reference. Additionally, there is nothing in the reference that would suggest how to make changes to the chemical compounds disclosed in the reference so as to arrive at the presently claimed chemical compounds. Additionally, the second proviso for claim 1 distinguishes over the Han Wei *et al.* and Llinas-Brunet Montse *et al.* journal references cited in the PCT search report. Each of the references, the PCT published application and the two journal references, have been previously identified in Information Disclosure Statements filed in the present application.

Regarding the use of such provisos, the Examiner's attention is invited to the decision *In re Johnson*, 558 F.2d 1008 (CCPA 1977), particularly the discussion regarding the rejection under § 112, beginning at page 1017, wherein the court states, "(i)nventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable." (*Id.*, 1018, citing *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976)) In particular, in the instant application as in *Johnson*, Applicants "are merely excising the invention of another, to which they are not entitled." (*Id.*, 1019) Accord, *Ex Parte Hughes*, 377 PTCJ A-9

(POBA, 1978). It is respectfully noted that in the alternative, Applicants could introduce at least several additional independent claims, setting forth permutations and combinations of generic moieties to accomplish the same result, albeit much less efficiently and requiring significant additional effort to examine and prosecute. Entry and consideration of the amendment is respectfully requested.

New method claims 95-107 have been added. These claims are supported by the specification and claims as filed. Entry and consideration of the claims is respectfully requested.

Claims 1-28, 30-35, and 51-66 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as claims 1-34 and 50-64 of copending U.S. Serial Number 09/908,955. The Examiner further states, "claims 1-28, 30-35, 51-66 are identical to claims 1-34, 51-66 (sic 50-64)." However, it is stated that the double patenting rejection is provisional "since the conflicting claims have not in fact been patented." The Examiner further states that a statutory type double patenting rejection cannot be overcome by a terminal disclaimer but, "can be overcome by canceling or amending the conflicting claims so that they are no longer coextensive in scope." Applicants have elected not to cancel or amend any of the claims referred to at this time since, as the Examiner noted, none of the conflicting claims have been patented. Applicants will take appropriate action with regard to the conflicting claims at such time as it becomes necessary to do so.

Claims 40-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39-43 of copending U.S. Serial Number 09/908,955. The Examiner explains that compounds in

claim 40, from page 631 to page 665 of the present application, are identical to compounds in claim 39 of the copending application. Furthermore, claims 51-66 and 68-93 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending U.S. Serial Number 09/908,955. The Examiner explains that compounds in claims 51-66 and 68-93 of the present application fall within the scope of general structure formula (I) of claim 1 of the copending application. As these obviousness type double patenting rejections are also provisional, Applicant will address them when allowed claims in the applications so require.

However, it is noted that there appears to be an inconsistency between the statutory type double patenting rejection of claims 51-66 recited on page 3 of the present Office Action and the obviousness type double patenting rejection of the same claims on page 10 of the Office Action. Before Applicants can address the rejection of claims 51-66 it will be necessary for Patent Office to clarify basis for the rejection.

The Office Action states, "Claims 1-35 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for compounds in table 1, (pages 43-51), table 2 (pages 289-340), table 3 (pages 144-182), table 4 (pages 365-429) and table 5 (429-595) does not reasonably provide enablement for all the compounds suggested by the general structural formula of claim 1. The Patent Office explains that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims." (Office Action, pages 3-4) This rejection is traversed.

In support of the rejection, the Patent Office cites and reviews various aspects of the decision *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In particular, the Patent Office briefly reports the holding of the Court in the decision and then reviews in detail the so-called "*Wands* factors" 1-8 set forth by the court, on pages 4-9 of the Office Action. For convenience these factors will be similarly referred to by number and comments will be provided in response to the Patent Office's remarks relating thereto. The court addressed these factors on its way to reaching a conclusion as to whether undue experimentation was necessary in the case at bar and in the context of the "enablement" requirement under the first paragraph of 35 U.S.C. §112. In particular, the court stated, "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Id., 8 USPQ2d 1404)

The first factor, "the breadth of the claims", is stated by the Patent Office to be presented by the general structure formula (I) of claim 1.

The second factor, "the nature of the invention", is said to be "a novel class of pharmaceutical compounds that are inhibitors of Hepatitis C Virus (HCV) protease activity, specifically compounds that inhibit HCV NS3/NS4a serine protease activity."

Regarding the third factor, "the state of prior art," the Patent Office acknowledges that, with regard to the general structure formula (I) of claim 1, "the prior art does not provide any evidence of HCV protease inhibitory activity-

specifically with regard to HCV NS3/NS4a serine protease inhibitory activity."

The Patent Office states that "the relative skill in the art" (factor 4) as it relates to the subject pharmaceutical compounds, is that of "a M.D. or Ph. D. level individual." Applicants take no exception at this time to the Patent Office's summary of *Wands* factors 1-4 as set forth above.

In discussing the "level of predictability in the art," the Patent Office states, "(s)ince the prior art does not teach that the compounds presented by general formula (I) of claim 1 formerly existed, the level of predictability is low in regards to the compounds of the invention with respect to HCV serine protease inhibitory activity." The Patent Office concludes, "(t)herefore, one of skill in the art would not be able to readily anticipate the inhibitory effects of the compounds of the invention in view of HCV NS3/NS4a serine protease inhibitory activity." (Office Action, page 6)

While apparently reasonable on its face, the Patent Office's conclusion with regard to predictability does not take into consideration Applicants' teachings. Certainly, Applicants' teachings cannot be used against them but they are considered under the heading of *Wands* factor 6 (the amount of guidance present). By characterizing the level of predictability as being "low" the Patent Office implies that one of skill in the art would be unduly burdened when faced with a determination of whether or not a compound within the scope of formula (I) of claim 1 would have the requisite inhibitory activity. However, having the benefit of Applicants' comprehensive teachings, one of skill in the art will have learned that the a significant number of compounds within the scope of general formula (I) of claim 1 have exhibited the

requisite inhibitory activity and, therefore, such a person would expect that such compounds will "predictably" have the desired response. Consequently, while the prior art is lacking with regard to a teaching sufficient to allow prediction of the performance of the compounds of formula (I) of claim 1, Applicants' teachings provide sufficient further knowledge allowing one of skill in the art to predict the performance of the claimed compounds, or at least to expect that such compounds will exhibit the requisite performance as claimed.

With regard to the "amount of guidance present" (*Wands* factor 6), the Patent Office states, "(t)he applicants have not provided guidance for all the compounds presented in the general formula (I) of claim 1." (Office Action, page 6; emphasis supplied) By charactering factor 6 in such a narrow manner, the Patent Office implies that Applicants must present results for all of the compounds of general formula (I) of claim 1 in order to reasonably satisfy this requirement. On the other hand, if the Patent Office is suggesting that Applicants should provide guidance sufficient to apply to all of the compounds presented in the general formula (I) of claim 1, it is respectfully suggested that Applicants have explicitly done so.

It is respectfully suggested that the operative word in *Wands* factor 6 is "guidance." Specifically, the summary of the factors appearing on page 4 of the Office Action states, "(6) the amount or direction or guidance presented;" it is noteworthy that the statement makes no *a priori* requirement that total guidance be provided. In fact, it is an evaluation of the amount of guidance provided that is the subject of the inquiry.

In the present application, Applicants include a series of tables identifying 1,908 individual compounds within

the scope of the claims that were synthesized and including performance data on a substantial number of these, as follows:

Table Number and Description	Number of Compounds
1: Compounds and HCV Protease Continuous Assay Results	362
2: Compilation of Example No. and Structure Synthesized	362‡
3: Compounds Prepared by Solid Phase Synthesis and Ki* Range	310
4: Additional Synthesized Compounds, Compound Name and Ki* Range	90
5: Additional Synthesized Compounds, Molecular Weight and Ki* Range	789
6: Synthesized Inhibitors‡‡	357
Total	1,908

‡ Same compounds as in Table 1 (Not included in total)
‡‡ Synthesized using various intermediates described in preparative examples

It is easy to gloss over the extensive disclosure provided by Applicants by briefly identifying several tables of results, but the full scope of their teachings can more readily be appreciated by explicitly detailing its content, as follows:

Applicants describe general preparative schemes starting on page 97, "methods of synthesis of intermediate building blocks" and continue with schemes 1-20, ending on page 110. This is followed with actual preparation of intermediates including enumerated steps, conditions and materials. Preparative examples 1-17 are described, concluding on page 129. Continuing with their guidance on how to prepare the compounds of the invention, the Applicants describe the solid phase synthesis, including the general procedure for solid-phase coupling reactions and Dess-Martin oxidation. This is followed by preparative examples 18-19 concluding on page 133. Scheme 8 then provides specific exemplification for a compound identified as 301J and then, reciting specific "moieties for the various functionalities in the compound of Formula I (Claim 1), the 310

compounds in Table 3 were prepared." (page 135) This is followed by explicit guidance starting on page 182 for "synthesis of intermediates for the compounds in Tables 4, 5 and 6 (1,236 different compounds), reciting materials, conditions, reaction sequencing, and analytical proof of results. This disclosure continues to page 360 of the application, comprising more than 178 pages of guidance. Applicants thereafter describe the specific methods used to perform the separation of diastereomers and the methods required to assay for HCV protease inhibitory activity according to techniques well-known to those skilled in the art to which the invention pertains. Applicants identify the specific references that were employed, as well as an explanation of the means by which they applied the referenced techniques to the claimed invention. These methods can be applied to every compound synthesized according to the extensive teachings provided by Applicants, including materials needed, enzyme preparation, substrate synthesis and purification, obtaining spectra of substrates and products, protease assay, evaluation of inhibitors and inactivators and the specific method for determining Ki* values reported.

As stated *In re Wands*, "*Wands'* disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." (*Id*, 1406) Clearly, as evidenced by the referenced pages above, the same facts and circumstances apply to the presently claimed invention.

In its evaluation of the data presented by Applicants, the Patent Office notes that "applicants have provided results of a HCV protease continuous assay for a group of compounds wherein applicants have categorized the Ki values associated

with each investigated compound as a barometer of HCV serine protease inhibitory activity." (Id., page 6, last paragraph to page 7, line 1; emphasis supplied.) After reciting values for the three ranges used in the tables, the Office Action states, "(w)ith such an apparent wide range of HCV protease activity it is pertinent that the applicants disclose further experimentation to show to a person skill(ed) in the art the level of potency for a given compound of the invention. Such information is required by a person skill(ed) in the art in order to be able to use the correct amount of the compound of the invention in a process such as an assay or a method of treatment." (Id.) Applicants take exception to this very stringent and narrow view of the "guidance" factor presented by the court in *In re Wands*.

It is accepted law that an applicant need not provide a manufacturing blueprint in a patent application in order for the patent application to form a basis for carrying the invention forward into practical applications and for the applicant to be entitled to broad claim coverage. Considering the relative level of skill in the art acknowledged by the Patent Office, a person with the degree of Medical Doctor or Ph.D., it is not unreasonable to expect that, once knowing that a compound, or class of compounds, exhibits serine protease inhibitory activity, such a person will have the requisite level of skill to be able to conduct routine experiments to establish a desirable dosage regimen for a particular compound that will be appropriate for a person in need of such treatment. As stated by the Office, Applicants have provided evidence in the form of a "barometer" of performance, and this is sufficient in order to lead a person of skill in the art to be able to select, synthesize, and characterize a particular compound within the

scope of the claims and have a reasonable expectation of success.

Significantly, it should also be recalled that the claims are directed to active compounds, e.g., exhibiting hepatitis C virus protease inhibitory activity. In this regard it is acknowledged by the Patent Office, "(t)he invention is a novel class of pharmaceutical compounds that are inhibitors of Hepatitis C Virus (HCV) protease activity" and "the prior art does not provide any evidence of HCV protease inhibitory activity-specifically with regards to HCV NS3/NS4a serine protease inhibitory activity." (Id., page 5, "2.The nature of the invention" and page 6, "3. The state of prior art.")

In other words, contrary to the view expressed by the Patent Office, it is not reasonably incumbent upon Applicants, under the heading of "guidance" to disclose further experimentation to show the level of potency for a given compound in order to use the correct amount in an assay or in a method of treatment. On the contrary, Applicants have provided significant guidance for the synthesis, characterization and performance of a large number of compounds within the scope of the claims, demonstrating that such compounds exhibit HCV protease inhibitory activity. In particular, Applicants teach that, in view of the ranges of Ki* values exhibited, the compounds of the invention have "excellent utility as NS3-serine protease inhibitors" (page 364, line 10).

Overall, the Patent Office has provided no basis on which to conclude that the teachings of the application would not be generally applicable to all compounds within the scope of the claims, whereas Applicants have clearly demonstrated that their synthesis methods and screening techniques, set forth in substantial detail in the application and in the associated art,

are generally applicable to compounds within the full scope of the claims. With all due respect, Applicants have met their burden with regard to providing guidance.

Under category "7. The existence of working examples." (*Wands* factor 7), the Patent Office states, "(h)owever, the specification does not provide working examples of all compounds suggested by the general structure formula (I) of claim 1." (Office Action, page 8, emphasis supplied) Contrary to this view, the law does not require working examples of all compounds suggested by a claimed generic structure. In fact, the *Wands* decision sets forth a series of factors to be considered, and also as presented and discussed in the Office Action, explicitly because experimental evidence is not required for all compounds claimed by an inventor.

Finally, with regard to *Wands* factor 8, "(t)he quantity of experimentation necessary," the Patent Office begins its analysis with a conclusion, "a large quantity of experimentation would be required in order for a person of skill in the art to be able to practice the invention, since there are a multitude of possible compounds that are suggested by the general formula of claim 1 and each compound needs to be tested for HCV protease inhibitory activity." (Id., page 8)

On the contrary, by presenting experimental evidence relating to a determination of Ki*, Applicants have presented a significant amount of experimental evidence regarding the inhibitory activity of the claimed compounds and, therefore, how such compounds are to be used. In other words, given that a compound inhibits HCV NS3 serine protease, one of skill in the art would expect it to have the requisite utility in the treatment of HCV. Furthermore, Applicants have clearly set forth several synthesis schemes and evaluation methods

(including methods and information described in the prior art and applicable to the claimed invention) for both making and using the claimed compounds.

Consequently, although such synthesis and testing methods may be complex, they are, in view of the comprehensive teachings of the application, and with reference to methods known in the art, merely routine and certainly within the skill of one in the art, a M.D. or Ph.D. As observed in *In re Wands*, "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (*Id.* 1404; emphasis supplied.) It is respectfully suggested that, especially in view of *In re Wands*, Applicants are entitled to the full scope of the claims as set forth by the general structure formula (I) of claim 1. Withdrawal of this rejection of the claims is respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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